Hemorrhage During Long-Term Anticoagulant Drug Therapy

Part II. Gastrointestinal Hemorrhage

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■ *Most of the gastrointestinal hemorrhages occurring during long-term anticoagulant drug therapy of 2,013 patients (reported in the literature) were caused by underlying lesions (44 of 77). Of the 44 lesions, only seven were diagnosed before treatment was started.*

Most of the episodes of hemorrhage occurred with the prothrombin activity at a so-called "safe" level. Closer investigation before the anticoagulant therapy was begun might have brought the underlying lesion to light.

GASTROINTESTINAL HEMORRHAGE is second to intracranial hemorrhage as the most serious bleeding complication during long-term anticoagulant therapy. Although it occurs more frequently and often is catastrophic in onset and severity, the mortality rate is low.[1] Controlled clinical trials have shown that anticoagulant drugs increase both severity and the incidence of gastrointestinal hemorrhage,[2,3] while similar studies of intracranial hemorrhage indicate that the use of anticoagulant drugs increases only the severity of the bleeding.[2,3]

This presentation is based on reports of 2,013 patients receiving long-term anticoagulant drug therapy (Table 1).[4-11,13-18] Some cases were reported as isolated instances and so were not analyzed in relation to the incidence of other hemorrhages.[1] There were 77 gastrointestinal hemorrhages (3.8 per cent) manifested by hematemesis or melena. The following questions are analyzed in this study:

1. What was the relation of gastrointestinal hemorrhage to underlying lesions? How many lesions were recognized before treatment?

2. What is the relation of hypocoagulability in general to gastrointestinal hemorrhage?

3. What was the relation of gastrointestinal hemorrhage to "low" prothrombin determinations?

4. How many of the lesions could have been diagnosed before treatment?

What Was the Relation of Gastrointestinal Hemorrhage to Underlying Lesions?—In the 77 reported patients with bleeding episodes, causative lesions were diagnosed in 44 (Table 1). These were: peptic ulcer, 22; neoplasm, 8; diverticulitis, 4; hiatal hernia, 3; acute gastritis, 3; cirrhosis of the liver, 2; "inflammation," 2. The only lesions diagnosed before hemorrhage, however, were seven peptic ulcers. In eight of the 15 patients with peptic ulcers diagnosed only after hemorrhage, the diagnosis was based on roentgenographic studies and in seven cases it was made presumptively because of a typical history. In the 22 cases in which causative lesions other than peptic ulcer were diagnosed, the diagnosis apparently was made

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TABLE 1.—*Data from the Literature on Gastrointestinal Hemorrhage During Long-Term Anticoagulant Drug Therapy*

Authors	*Cases Treated*	*Gastro-Intestinal Hemorrhage*	*Causes Given*	*Lesions Causing Hemorrhage*	*Identified Before or after Hemorrhage*
Tulloch and Wright[15]	227	6	2	Acute Gastritis Hiatal Hernia	After
Pollard, et al[11]	139	5	2	Duodenal Ulcer, both cases	Not stated
Nichol and Borg[9]	78	2	1	1 Duodenal Ulcer (1 Case x-ray after: negative)	Before .....
Suzman[14]	82	1	Not stated	Not stated	.....
Keyes, Drake and Smith[7]	121	3	Not stated	Not stated	.....
Pickering[10]	195	2	2	2 Peptic Ulcer	After
Bjerkelund[2]	119	7	7	4 Peptic Ulcer 1 Gastritis 1 Hiatal Hernia 1 Gastric Carcinoma	3 Before 4 After
Fisher[5]	195	8	7	7 Peptic Ulcers	After (by history)
Groch et al[6]	92	8	5	3 Neoplasm 2 Inflamm.	After
Borchgrevink[3]	103	3	3	1 Alcoholic Gastritis 1 Peptic Ulcer 1 Cirrhosis of Liver	1 Before "Hematemesis"
Waller[17]	275	11	2	2 Duodenal Ulcers	Before
Whittier et al[18]	54	8	3	1 Esophageal Varices 1 Duodenal Ulcer 1 Carcinoma of Colon	After
Stephens[13]	181	3	3	2 Diverticula 1 Gastric Carcinoma	After
Moseley[8]	62	6	5	2 Carcinoma of Colon 1 Diverticulitis 1 Duodenal Ulcer 1 Hiatal Hernia	After
Udall[16]	57	1	0	(Negative x-ray)	
Drinan et al[14]	33	3	2	1 Peptic Ulcer 1 Diverticulitis	After
TOTALS	2013	77	44		After 37 Before 7

from roentgenographic examinations. Among the 33 patients with no causative lesions detected, 15 had roentgenographic studies. Thus, causative lesions were found in nearly three out of four cases in which roentgenographic studies were made (37 of 52). The proportion of demonstrable lesions in studies of gastrointestinal hemorrhage occurring during short-term therapy is reported to be much lower.[19] Only seven out of 24 patients had demonstrable gastrointestinal lesions.

What Is the Relation of Hypocoagulability in General to Gastrointestinal Hemorrhage?—Controlled clinical trials leave little doubt that gastrointestinal hemorrhage occurs more frequently in a group of patients receiving anticoagulant drugs than in a control group.[2,3]

There is no precise test to determine the point at which failing coagulation will permit mild bleeding to become severe. A patient with normal coagulation obviously can have a massive hemorrhage if an ulcer erodes a large blood vessel. The primary determinant of hemorrhage, thus, is not the coagulability of the blood but the nature of the vascular lesion.

For valid correlation of hemorrhage with clinical levels of prothrombin activity, it is necessary to know how much of the time during the total treatment period the prothrombin value was above and how much of the time below the "safe" level. The "safe" level was considered to be at or about 10 per cent by the prothrombin-proconvertin test or 20 per cent by the Quick one-stage test.[1] A low level observed after the onset of hemorrhage may be not the cause of the bleeding but the result of massive loss of blood which rapidly depletes the many thrombotic elements.

What Was the Relation of Gastrointestinal Hemorrhages to "Low" Tests?—Four studies were re-

TABLE 2.—*Frequency of Spontaneous Gastrointestinal Hemorrhage in Long-Term Anticoagulant Drug Treatment in Relation to Times the Prothrombin Activity Was Below the "Safe" Level*

Authors	Diagnosis	Patients	Prothrombin Tests* Total	At "Safe" Levels	Below "Safe" Levels No.	Below "Safe" Levels Per Cent	Gastrointestinal Hemorrhage With number of Deaths in Parentheses: At "Safe" Levels	Gastrointestinal Hemorrhage With number of Deaths in Parentheses: Below "Safe" Levels
Bjerkelund[2]	Myocardial Infarction	119	11649	10654	995	8.5	2 (0)	5 (0)
Borchgrevink[3]	Angina Pectoris	103	2428	2115	313	12.9	1 (0)	1 (0)
Moseley[8]	Various	300	2668	2454	214	8.0	6 (1)	0
Askey[1]	Various	100	4326	3863	463	10.6	1 (0)	1 (1)
Totals		662	21071	19086	1985	9.4	10 (1)	7 (1)

*Average interval between tests: Bjerkelund 1 to 3 weeks. Others, 4 weeks.

viewed in which all the prothrombin levels were stated during the total period of long-term treatment (Table 2). In 622 cases, 21,071 tests were made. In 1,985 test periods in which prothrombin was below the "safe" level, seven gastrointestinal hemorrhages occurred; in 19,086 "safe" periods, 10 bleeding episodes occurred. Lesions were demonstrated in all seven patients who had bleeding below "safe" levels and in nine of the 10 who bled at "safe" levels. Among those whose prothrombin level was determined only after onset of hemorrhage, the correlation was comparable although not identical. There were 31 such patients in whom the cause of hemorrhage was demonstrated; in 20 of them the results of tests were at or above the so-called "safe" level (20 per cent Quick); in 10 of them below that level and in one equivocal (Table 3). It must be remembered that the "low" readings may have been the result of the bleeding and not the cause. Therefore the number

TABLE 3.—*Relation of Prothrombin Activity to Gastrointestinal Hemorrhage With Underlying Lesions*

Authors	Number of Cases	Lesions	Prothrombin Activity (After Hemorrhage): In "Therapeutic Range"*	Prothrombin Activity (After Hemorrhage): Below "Therapeutic Range"†
Tulloch and Wright[15]	2	1 Acute Gastritis 1 Hiatal Hernia	20 seconds (Quick) Equivocal ("25 to 40 sec.")	
Pollard et al[11]	2	Duodenal Ulcer	1, 19 seconds 1, 32 seconds (Control, 17 to 19 seconds)	
Nichol and Borg[9]	1	Duodenal Ulcer		35 Seconds (15% Quick)
Bjerkelund[2]	7	4 Peptic Ulcer	1, Duodenal Ulcer, 11% PP	3 Peptic Ulcers (5%, 5% and 3% PP)
		1 Hiatal Hernia 1 Gastric Cancer 1 Gastritis	1, Hiatal Hernia, 10% PP	1 Gastric Cancer (3% PP) 1 Gastritis (7% PP)
Fisher[5]	4	Duodenal Ulcers	1, 28 Seconds (Quick)	1, 41.6 Seconds (Quick) 1, 150 Seconds (Quick) 1, 2% (Quick)
Groch, McDevitt and Wright[6]	5	3 Neoplasm 2 "Inflammation"	Inferred	
Borchgrevink[3]	3	2 Duodenal Ulcers 1 Esophageal Varix	1, 15% PP 1, 55% PP	1 Gastritis, 5% PP
Mosley, et al[8]	5	2 Colon Cancer 1 Diverticulitis 1 Duodenal Ulcer 1 Hiatal Hernia	"Not excessive"	
Drinan, et al[4]	2	1 Duodenal Ulcer 1 Diverticulitis	"In therapeutic range"	
Totals	31		20 (1 equivocal)	

*At or above 10 per cent by prothrombin-proconvertin (PP) test or 20 per cent by Quick test.
†Below 10 per cent by prothrombin-proconvertin (PP) test or 2 per cent by Quick test.

of hemorrhages occurring at "safe" levels would be, if anything, higher.

Zweifler[19] reported comparable results in short-term anticoagulant therapy: Of seven patients with hemorrhage from demonstrated organic lesions, five had onset with prothrombin at or above 20 per cent (Quick test); of 16 gastrointestinal hemorrhages occurring at levels lower than 20 per cent, only two were due to lesions that could be detected roentgenographically. In other words, most of the patients with gastrointestinal hemorrhage in whom underlying gastrointestinal lesions could be demonstrated bled with the prothrombin activity at a so-called "safe" level. This was also true in recent reports.[8,12] The occurrence of only seven gastrointestinal hemorrhages during 1,985 periods when the Quick one-stage test was below 20 per cent hardly identifies this as an "unsafe" level.

How Many of the Lesions Could Have Been Diagnosed Before Treatment?—It is probable that most of the 44 lesions diagnosed after the hemorrhage could have been detected before the anticoagulant treatment was begun. Systematic search for such lesions before treatment was not reported in most of these studies. Many times the history recorded before treatment did not lead to suspicion of ulcers, although more intensive questioning following hemorrhage elicited a history of significant symptoms.[5] Many more of the 44 lesions that caused bleeding probably could have been identified (had they been suspected) from a more thorough inquiry and investigation before hemorrhage. Earlier recognition would ensure closer observation during treatment and would probably prevent many serious hemorrhages. Search for blood in the stool is a prerequisite to anticoagulant therapy, but in most of these patients it was not reported. The clinicians' uncertainty as to the accuracy and significance of stool tests for blood undoubtedly is responsible. If pre-treatment stool tests are repeatedly positive for blood, however, a thorough gastrointestinal investigation should be undertaken, even in the absence of symptoms.

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REFERENCES

1. Askey, J. M.: Hemorrhage during long-term anticoagulant drug therapy. Calif. Med. To be published.

2. Bjerkelund, C. J.: The Effect of Long-Term Treatment with Dicumarol® in Myocardial Infarction, Grune & Stratton, Inc., 1957.

3. Borchgrevink, C. F.: Long-term anticoagulant treatment in angina pectoris and myocardial infarction, Acta med. Scandinav. Suppl., 359, Accomp., Vol. 168, 1960.

4. Drinan, F. W., Adamis, D., Sise, H. S. and Moloney, W. C.: Studies on the anticoagulant phenindione. III. Its use in ambulatory patients, Am. Heart J., 53:284, February 1957.

5. Fisher, C. M.: Anticoagulant treatment in cerebral thrombosis and cerebral embolism, Neurology, 11:119, April 1961.

6. Groch, S. N., McDevitt, E. and Wright, I. S.: Long-term study of cardiovascular disease, Ann. Int. Med., 55:358, September 1961.

7. Keyes, J. W., Drake, E. H., and Janney-Smith, F.: Survival rates after myocardial infarction with long-term anticoagulant therapy, Circulation, 14:254, August 1956.

8. Mosley, D. H., Schatz, I. J., Breneman, G. M. and Keyes, J. W.: Long-term anticoagulant therapy, J.A.M.A., 186:914, 7 December 1963.

9. Nichol, E. S., and Borg, J. F.: Long-term Dicumarol® therapy to prevent recurrent coronary artery thrombosis, Circulation, 1:1097, May 1950.

10. Pickering, G. W.: Clinical Problems and Results. Controlled Clinical Trials, Charles C Thomas, Springfield, Ill., 1960, p. 115.

11. Pollard, J. W., Hamilton, M. S., Christensen, N. A., Achor, R.W.P.: Problems associated with long-term anti-coagulant therapy, Circulation, 25:311, February 1962.

12. Schatz, I. J., and Keyes, J. W.: Long-term anticoagulant therapy, Complications and control of 978 cases. Anticoagulant therapy in Ischemic Heart Disease, Miami Heart Institute Symposium, Grune and Stratton, New York, 1965. p. 157.

13. Stephens, C. A. L., Jr.: Anticoagulant therapy in private practice, Circulation, 9:682, 1954.

14. Suzman, M. M., Ruskin, H. D., and Goldberg, B.: An evaluation of the effect of continuous long-term anticoagulant therapy on the prognosis of myocardial infarction, Circulation, 12:338, September 1955.

15. Tulloch, J., and Wright, I. S.: Long-term anticoagulant therapy. Further experiences, Circulation, 9:823, June 1954.

16. Udall, J. A.: The establishment and operation of a long-term anticoagulation clinic, Am. J. M. Sc.,244: 214, August 1962.

17. Waaler, B. A.: The effect of permanent anticoagulant treatment on symptoms and morbidity in angina pectoris, Acta med. Scandinav., 157:289, 1957.

18. Whittier, J. R., Korenyi, C., Klein, D. F., and Foley, W.: Prevention of degenerative disease: A controlled study of anticoagulant prophylaxis, J. Chron. Dis., 14:203, August 1961.

19. Zweifler, A. J.: Relation of prothrombin concentration to bleeding during oral anticoagulant therapy, New Engl. J. Med., 267:283, 9 August 1962.